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Research report

Dopamine mediation of the feeding response to violations of spatial and temporal expectancies

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Abstract

The present studies were aimed at further characterizing the role of DA in motivation. Rats, conditioned to expect food in one environment and no food in another, all received food on the test night. Those in the environment in which food was unexpected ate four times as much as those eating where food was expected. The overeating was eliminated by administration of the D2 antagonist raclopride. Another expectancy, timing of light offset in rats entrained to a fixed light–dark cycle, was violated by unexpectedly turning the lights off 1 h early. This provoked an elevation in food intake, which was also eliminated by the administration of raclopride. Feeding in two other situations not involving violation of expectancies (food deprivation; normal light offset) was unaffected by DA antagonism. These findings support the idea that DA signals errors in expectancy and that DA signaling is necessary for certain behavioral responses to unexpected events.

Keywords: Dopamine; Feeding; Reward; Motivation; Deprivation; Circadian

1. Introduction

Behavior directed at obtaining rewards is critical to survival. The neurotransmitter dopamine (DA) and its target sites in the striatum and nucleus accumbens (NAC) have been implicated in reward-related behavior. Initially it was proposed that DA transmission mediated the positive reinforcement associated with rewards [35]In support of this notion, DA antagonists have been shown to decrease behavior aimed at obtaining a variety of rewards including drugs of abuse and food [6,33]. Additionally, it has been repeatedly demonstrated that DA transmission increases during instrumental responding for rewards [18,24]. However, DA antagonists fail to block all forms of motivated behavior [17,29]. Furthermore, DA transmission fails to respond each and every time a reward is delivered [5,8,16,24,28]. Indeed, Di Chiara and colleagues have observed increased DA efflux in the NAC in response to presentation of a novel, palatable food but, only upon its first presentation. Subsequent presentations fail to elicit a DA response [1]. These, as well as a number of other findings [3], are inconsistent with the original form of the DA reward hypothesis. Different laboratories using different species, techniques and behavioral paradigms have generated multiple theories in order to refine our understanding of the role of DA in reward-related behavior [3,8,29,31].

One theory, generated from a programmatic effort to characterize the responses of individual dopamine neurons during classical conditioning and instrumental responding emphasizes a motivational role for DA during learning [31]. Schultz and colleagues have characterized the responses of individual DA neurons in awake and behaving primates during the presentation of rewards and stimuli that predict the occurrence of reward [18,31]. The preferential activation of DA neurons to unpredicted or unexpected delivery of rewards and the

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decrement in neuronal responses when rewards unexpectedly fail to occur, following associative learning, have led to the more specific theory that DA signals errors in reward prediction [31]. Unexpected events, particularly those having consequences for survival, are important to animals and are the occasions for learning. The proposed error signal generated by DA neurons is thought to drive learning [21,31].

The present studies were aimed at examining the theory that DA signals errors in expectation using pharmacological manipulations in two new behavioral paradigms. The studies use feeding behavior as a model system in which rats are trained to develop a set of spatial or temporal expectancies about their environment. When tested in situations where their expectancies were violated, significant increases in food intake are provoked. The increased food intake specific to situations in which expectancy was violated was found to be completely blocked by administration of a DA D2 receptor antagonist, while food intake in other situations were unaffected by D2 antagonism. These studies focus on D2 receptors because the D2 receptor is expressed both pre-synaptically on DA neurons and post-synaptically on NAC neurons [15,32] — a region that has been implicated in motivation for decades [19,25]. In addition, the D2 receptor has been proposed to be preferentially involved in feeding [12]. These studies lend support to the emerging hypothesis that DA signals errors in expectation.

2. Materials and methods

2.1. Subjects

Male Long Evans rats (University of Washington Psychology Dept. Breeding Colony), 325–375 g, were used in all experiments. Rats were maintained on a 12:12 light/dark cycle with dark phase onset occurring at 21:00 h in experiments 1 and 2 and 18:00 h in experiments 3 and 4. Food and water were available ad libitum except where otherwise noted. Experimental protocols conformed to institutional standards for animal care.

2.2. Violation of spatial expectancy

Prior work suggests that the unexpected availability of food in an environment previously associated only with food deprivation leads to a bout of overeating [27] (Van Dijk et al., unpublished data). The present study assessed the role of DA in this overeating response. Twenty-four rats were housed individually with wood chip bedding in plastic tubs ($50 \times 24 \times 20.5$ cm). Stainless steel covers supported water bottles and food. Two separate rooms were used as sites of distinctive conditioning environments. One environment consisted of the same plastic tubs with cat litter on the floor (Johnny Cat Fresh Scent) and almond odor added (10 drops of 1:10 almond extract/water). The other environment consisted of stainless steel hanging wire cages with water bottles attached with a spring. All environments had the same light/dark cycle. Following a 1-week acclimation to the home cage, rats were weighed for 5 days at which time conditioning began.

Ten conditioning trials occurred over a 49-day period. A trial consisted of a night (12-h dark phase) in which rats were removed from their home cage, weighed and placed in one of the two conditioning environments. Five trials were deprivation nights with all rats placed in one of the distinctive environments with water but no food for the duration of the dark phase. Five trials were no-deprivation nights with all rats placed in the other distinctive environment with food and water available ad lib for the duration of the dark phase. Half the rats were deprived in the tubs with cat litter and given food in the hanging metal cages. The other half had environmental pairings reversed. Three to 7 days in the home cage were interspersed between conditioning trials. The next conditioning trial did not commence until rats had stable body weights. The order of deprivation and feeding trials was determined semi-randomly such that no more than two trials of one type occurred consecutively.

The effects of violated expectancies about environment and food availability (spatial expectancies) were tested by placing all rats in one of the two conditioning environments, just before the start of the dark phase, and providing them with food. For half the rats, the environment was the one in which food had always been available (physical environments were counterbalanced). The other half of the group unexpectedly received food in the environment that had always been paired with food deprivation. Food intake was measured at 1, 2, 3 and 12 h. The role of DA in the rats' response to violations of their expectations was evaluated by administering the selective D2 receptor antagonist raclopride, (0.2 mg/kg i.p.; Sigma, St. Louis, MO) or vehicle (0.15 M NaCl i.p., 1.0 ml/kg) 15 min before the start of the dark phase. The specific antagonist used here was chosen for its effects, at low doses, on motivated behavior without effects on motor function [26,30]. Body weights of groups were matched and environments were counterbalanced. Thus, four groups were formed: (1) expect food/saline (Expected-Sal, $n = 6$); (2) expect food/raclopride (Expected-Rac, $n = 6$); (3) unexpected food/saline (Unexpected-Sal, $n = 6$); and (4) unexpected food/raclopride (Unexpected-Rac, $n = 6$).

2.3. Food deprivation

Twenty-four-hour food deprivation induces a robust feeding response when food is returned. Intake in the first hour is similar in magnitude to rats eating in the environment where they unexpectedly receive food. The contribution of DA to deprivation-induced feeding was assessed in 12, drug-naïve rats from experiment 1, tested 2 weeks after the conclusion of experiment 1. All rats were deprived of food, beginning just before light offset, for 24 h. After 23.75 h of deprivation, half the rats were injected with raclopride (0.2 mg/kg i.p.; $n = 6$) and the other half were injected with vehicle (0.15 M NaCl i.p., 1.0 ml/kg; $n = 6$). Food intake was measured 1 h after light offset.

2.4. Violation of temporal expectancy

Rats are more active and consume most of their food during the dark phase of the light/dark cycle. A large bout of feeding occurs at the time of light offset. Unexpected darkness during the light phase increases food intake [23]. In animals well habituated to a regular light/dark cycle, unexpectedly advancing light offset by an hour can promote a bout of feeding. The contribution of DA to this feeding response was assessed. Twenty naïve rats were housed singly in hanging wire cages. Water and food were made available ad libitum. Rats were maintained on a 12:12 light/dark cycle with light offset occurring at 18:00 h. Rats were acclimated to this environment for 1 week at which time a habituation period began. During habituation, rats were injected daily with 0.15 M NaCl (1.0 ml/kg) at $t = -1.25$ h relative to light offset. Food intake was measured for the hour just before and just after light offset. The 7th habituation session served as baseline data.

The effect of violation of temporal expectancies regarding light offset was tested by advancing light offset by an hour (17:00 h). Half the rats were injected with raclopride (0.2 mg/kg i.p.; $n = 10$) and half the rats were injected with vehicle (0.15 NaCl i.p., 1.0 ml/kg; $n = 10$). Injections were given at $t = -15$ min relative to the early light offset. Food intake was measured in each of the first 2 h of the dark phase.

2.5. Normal light offset

To determine if DA is involved in a large meal that occurs in response to normal, expected light offset, some of the rats from experiment 3 were used. Following the conclusion of experiment 3, rats were maintained in the same housing conditions for 2 weeks with a 12:12 light/dark cycle with light offset occurring consistently at 18:00 h. After this re-entrainment period, rats were habituated to injections of 0.15 M NaCl given at $t = -15$ min relative to light offset. The 3rd habituation session served as baseline data.

The contribution of DA to food intake when expectancies are not violated was tested by giving half the rats raclopride (0.2 mg/kg i.p.; $n = 5$) and half the rats saline (0.15 NaCl i.p., 1.0 ml/kg; $n = 5$). Each group included rats with one prior exposure to raclopride and drug naïve rats. Injections were given at $t = -15$ min relative to light offset and food intake was measured for the hour before and after light offset.

2.6. Statistical analysis

A commercial software package (SPSS; Chicago, IL) was used to evaluate the statistical significance of group differences. Parametric analyses (ANOVA, t-test) were used when data conformed to the assumptions of these tests. However, in some experiments (experiments 3 and 4), data were not distributed normally within groups. Therefore non-parametric statistics (Wilcoxin Signed Ranks, Mann–Whitney) were employed.

3. Results

3.1. Violation of spatial expectancy

Rats that received food in an environment in which they expected deprivation ate more than rats that received food in an environment where they expected it. Thus, the error in expectancy based on conditioning environment potentiated food intake. DA antagonism completely blocked the potentiated intake of rats that unexpectedly received food but had no effect on the intake of those who expected food. These observations were clearest during the first hour of the dark phase (see Fig. 1). During this time, there were significant main effects (two-way ANOVA) of environment (expect food vs. unexpected food, $F_{1,20} = 9.37$; $P < 0.01$), and injection (raclopride vs. saline, $F_{1,20} = 4.37$; $P = 0.05$), as well as a significant interaction of the two ($F_{1,20} = 7.02$; $P < 0.05$). The significant interaction suggested that raclopride reduced feeding only in one condition of expectancy. This was confirmed statistically by a post-hoc Tukey's test of all pairwise comparisons which indicated that saline injected rats eating in the environment in which food was not expected ate significantly more than all other groups while no other pairwise comparisons proved significantly different. There were no statistically significant differences in intake across groups during the second and third hours of the dark phase (Fig. 1), suggesting that the environmental influence on eating was short lived.

One factor that may have contributed to the difference in antagonist effectiveness between rats eating under different expectancy conditions was the greater food intake in the group that received food unexpectedly. The next study examined whether the same dose

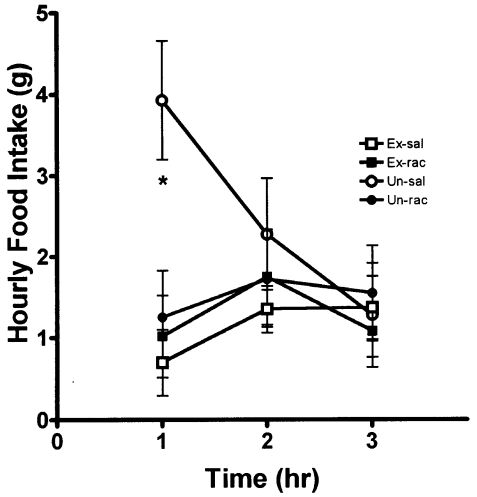

Fig. 1. Over-eating, in response to violation of spatial expectancy, is blocked by a D_2 antagonist. Hourly intake of rats, through the first 3 h of the dark phase, tested in either the environment where they expect food (squares) or do not expect food (circles). Rats were injected with either saline (open symbols) or raclopride (closed symbols). Data represent the mean ± S.E. ($*P < 0.05$).

of D2 antagonist would suppress comparable levels of food intake prompted by food deprivation.

3.2. Food deprivation

Rats deprived of food for 24 h consumed a large meal when food was returned at the start of the dark phase. As shown in Fig. 2, vehicle-injected and raclopride-injected rats ate comparable amounts, 5–6 g, of food in the first hour of the dark phase following 24-h food deprivation. Raclopride-injected rats, on average, ate only 1 g less than saline-injected rats, a difference which is likely attributable to chance ($t_9 = 0.52$; $P =$

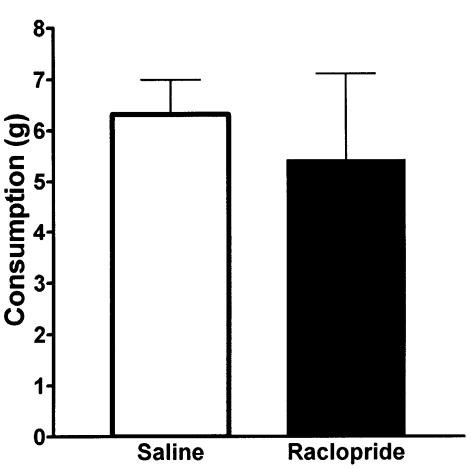

Fig. 2. Deprivation-induced feeding is not affected by D_2 antagonism. Rats were injected with either saline (clear bar) or raclopride before receiving food following 24 h of food deprivation. Data represent the mean ± S.E.

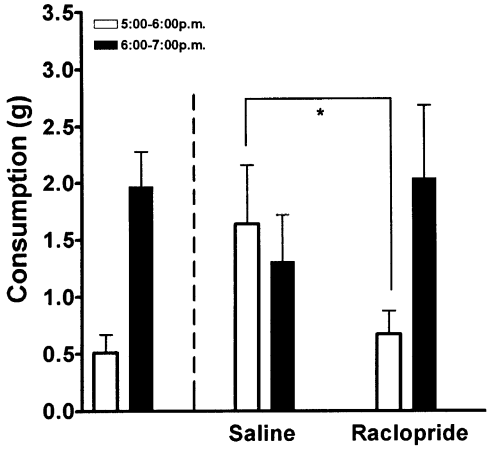

Fig. 3. Over-eating, in response to violation of temporal expectancy, is blocked by a D_2 antagonist. Left: food intake during the hour just before (clear bar) and after (black bar) expected light offset. Right: food intake during the first 2 h of the dark phase when light offset occurred 1 h earlier than expected. Data represent the mean ± S.E. ($*P < 0.05$).

0.61). It is important to note that both groups in this experiment had comparable intakes to saline-injected rats eating in the environment in which deprivation was expected. These results fail to support the idea that raclopride effects on food intake depend primarily on amount of food consumed. Instead, they suggest that it was the unexpected aspect of the feeding situation that led to its dependence on DA. The next study used another unexpected event, early light offset, to test this hypothesis further.

3.3. Violation of temporal expectancy

Rats maintained on a fixed light–dark cycle consume very little during the light phase and consume a large meal at light offset [23]. We confirmed these previous observations during the habituation phase of this experiment. Rats ate significantly more during the first hour of the dark phase (6:00-7:00p.m.) than during the hour preceding the start of the dark phase (5:00-6:00p.m.) (Wilcoxon Signed Ranks test ($Z = -3.66$; $P < 0.01$; Fig. 3, left).

When the room lights were turned off, unexpectedly, 1 h early (17:00 h), rats injected with saline ate significantly more food during that hour than they had the day before in the light ($U = 40.0$; $P < 0.01$, Mann–Whitney Test; see Fig. 3). Raclopride injected rats failed to show this feeding response (unexpected dark hour when compared to the same hour in the light the day before ($U = 94.0$; $P = 0.81$; see Fig. 3)). They also ate significantly less than saline injected rats, on the test day, during the first, unexpected hour of the dark phase ($U = 20.0$; $P < 0.05$). Thus, the unexpected event of early light offset promoted a feeding response that was

eliminated by DA antagonism. The final study examined whether the feeding response to expected light offset is similarly affected by the antagonist.

3.4. Normal light offset

Rats eating in response to an established, expected light offset time were unaffected by DA antagonism. Fig. 4 shows no difference between rats injected with saline just prior to light offset and rats injected with raclopride just prior to light offset. Thus, while the feeding response to expected light offset appears not to be DA dependent, DA does appear to be important for the feeding response to light offset when it is not expected.

4. Discussion

The present studies used two new behavioral paradigms to further define the role of DA in motivated behavior, with a particular focus on Schultz's theory about reward prediction. Key features of these paradigms are that expectations based on spatial and temporal cues are violated. In one instance, spatial cues predict either food availability or deprivation. In the other, temporal lighting cues exert control over a bout of intake. In both cases, on the test day when actual outcomes do not match expected outcomes based on previous associations, food intake is greatly stimulated. Furthermore, in both cases, this increased food intake following violations of expectancies is completely blocked by antagonism of D2 receptors. We also examined two situations (24-h food deprivation and normal light offset) where feeding is stimulated without any violation of expectancies. In both of these instances, the same dose of DA antagonist that affected feeding in response to violations of expectancies had no effect on intake. All studies employed the selective D2 receptor antagonist raclopride and therefore the receptor specificity of the effects demonstrated remains to be determined. The findings presented here provide an important framework for defining some of the conditions in which DA is critically involved in the motivated behavior of feeding.

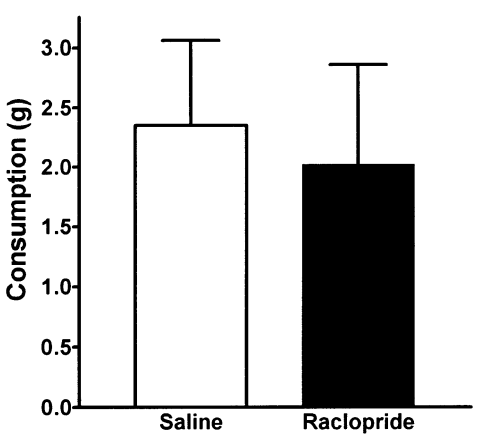

Fig. 4. Feeding in response to expected light offset is not affected by D_2 antagonism. Data represent the mean ± S.E.

Recently, the idea that DA is critical for mediating the rewarding aspects of positively motivating stimuli (i.e. intracranial stimulation, drugs of abuse, sex and food) has undergone re-evaluation. Several findings have fueled this shift. Near total destruction of mesolimbic and nigrostraital DA neurons leave typical oral–facial responses to rewarding stimuli intact [3] suggesting that rats are capable of evaluating the rewarding properties of stimuli without the benefit of DA signaling. In addition, activation of DA systems during the expression of motivated behavior is not always observed during the consumption of rewards [5,16,24]. DA activation changes in its temporal expression or is not expressed at all in response to rewards when they are cued or when animals have control over reward delivery [9,18,24]. Finally, DA antagonists are effective in blocking motivated behavior under some circumstances [11,30,35] but not others [4,17,29]. An explanation of these inconsistencies has remained elusive.

Schultz and colleagues have put forth a theory, based primarily on a body of evidence derived from electrophysiological recordings of DA neurons in awake and behaving primates, suggesting that activity in midbrain DA systems signals errors in reward expectation [31]. That is, when reward outcome does not match expected outcome, changes in DA transmission are provoked. When outcome is better than expected (as in unpredicted rewards), there is an increase in DA transmission whereas when outcome is worse then expected there is a decrease in DA transmission [18]. To date, essentially all support for this theory comes from Schultz's electrophysiological studies. The studies presented here represent the first to demonstrate that presumed DA release, as a consequence of errors in expectation, contribute importantly to goal-directed behavior. The present studies involved the feeding responses of rats with specific spatial or temporal expectancies about their environment. On the critical test day, when experimental outcome did not match expectation, normal DA function was found to be necessary for the elevated feeding response.

In experiment 1, rats were conditioned to expect food in one environment and no food in another. When all rats received food on the test night, those in the environment in which food was unexpected (violation of spatial expectancy) ate four times as much (in the first hour) as rats whose experience matched their expectancies. It is important to note that all groups experienced the same amount of deprivation in the same temporal order during conditioning. Thus, the only variation

between groups was the environment in which they were tested and, consequently, their learned expectancies. While increased intake in response to conditioned cues has been demonstrated before [34], to our knowledge, this finding represents the first demonstration of an increase in food intake based on violations of expectancies established through conditioning. The increased food intake in this situation was completely blocked by a D2 receptor antagonist while food intake in response to expected cues was unaffected by DA antagonism. Thus, food intake in one situation was dependent on DA but in the other it was not. Based on the work of Schultz and colleagues, we propose that the violation of expectancy in the former situation generated increased DA activity which contributed significantly to the increased feeding observed (see below).

Experiment 2 addressed the possibility that it was the high level of food intake provoked in one context but not the other that made it susceptible to interference by the DA antagonist. In experiment 2 food intake was provoked by food deprivation and intake was at least as high as in experiment 1 but the antagonist was without effect. Note that this is not intended to imply that DA plays no role in deprivation-induced feeding. Indeed, at higher doses, D2 receptor antagonists have been shown to inhibit deprivation induced feeding [12]. By using a low dose of the antagonist we identified situations in which the feeding response is particularly sensitive to interference with DA transmission. The main purpose of experiment 2 was to exclude the possibility that this low dose of raclopride induced malaise or motor impairment, and that such non-specific effects would emerge only when animals were eating a lot.

Experiment 3 used a second manipulation of expectancies to provoke a feeding response. Rats well entrained to a lighting schedule had the time of light offset unexpectedly advanced by 1 h. This manipulation prompted a four to fivefold increase in food intake during that hour relative to intake during the same hour the day before when the lights were on. Administration of the DA antagonist completely blocked the feeding response to the unexpected early darkness. Thus, violation of expectancy regarding the normal light–dark cycle led to robust feeding that was apparently dependent on DA signaling. Experiment 4 determined whether this effect was due to disruption of cue-initiated eating in general or was specific to the unexpected presentation of a cue. Food intake in response to expected light offset was found to be unaffected by DA antagonism. Taken together, this set of studies defines a set of conditions — namely violations of spatial or temporal expectancies — in which normal DA transmission is necessary for the feeding response.

One area of the NAC has been demonstrated to be involved specifically in food intake [13]. By either blocking glutamate receptors or stimulating GABA receptors in a region of the NAC shell, Kelley and colleagues have demonstrated the induction of robust feeding even in sated rats [2,14]. Thus, some decrement in neural excitability in the NAC can potently stimulate food intake. Interestingly, it has been demonstrated that DA action at the D2 receptor attenuates glutamate's excitatory influences on NAC neurons [7,20,22]. The present results are consistent with a framework provided by both Schultz and Kelley such that unexpected food presentation induces DA release in the NAC. DA, acting in part at the D2 receptor, inhibits glutamate's negative effect on feeding behavior thereby facilitating feeding. Pharmacological blockade of D2 NAC receptors prevents this.

Experiment 1 provides clear support for Schultz's theory that DA activity is involved in the response to errors in reward expectancy. On the other hand, in Experiment 3 the unexpected event was light offset not reward presentation. Thus, what experiments 1 and 3 have in common is an unexpected event that prompts a feeding response. In this sense, these data fit well with a more general view of the role of DA, namely that it is activated 'under conditions of salient environmental change' and may prepare the animal for high levels of behavioral activity [10]. In experiments 1 and 3 there was clearly a salient environmental change associated with increased feeding. The use of pharmacological blockade in the present studies convincingly demonstrated that the D2-mediated transmission stimulated by salient environmental change has behavioral relevance in that it is necessary for the robust feeding behavior observed when expectancies were violated. The present studies are important because they provide converging evidence in support of these theories using new and distinct experimental protocols.

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